

Network pharmacology for mechanistically redefined comorbidities

Citation for published version (APA):

Elbatrik, M. H. M. (2020). *Network pharmacology for mechanistically redefined comorbidities*. Gildeprint Drukkerijen. <https://doi.org/10.26481/dis.20200826me>

Document status and date:

Published: 01/01/2020

DOI:

[10.26481/dis.20200826me](https://doi.org/10.26481/dis.20200826me)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

10

SUMMARY

Diabetes, atherosclerosis, hypertension and stroke are common comorbidities and the leading causes of death and disability worldwide. Current therapies are symptom-oriented, do not target the underlying cause and are therefore imprecise. One main reason for this unmet medical need is that these complex diseases are defined by a symptom in an organ and not by a molecular mechanism. Network medicine, however, shows that within the diseasome these comorbidities relate to the same cluster and, thus, likely share common hidden causal pathomechanisms. Targeting these mechanisms would be preferred to symptomatic therapy and, since these mechanisms are small signalling modules, network pharmacology is preferable to single-target approaches. One example of such a causal signalling module is the reactive oxygen species (ROS) and cGMP signaling (ROCG) network.

Pharmacologically, several drug classes target this network, including NADPH oxidase (NOX) inhibitors and nitric oxide (NO) donors. In this thesis, a NOX inhibitor panel approach was successfully applied to pharmacologically validate the pathomechanistic involvement of a specific NOX isoform. In addition, NO-cGMP signalling was found to be halted by chronic elevation of NO as part of a chemical feedback loop that converts the NO receptor, soluble guanylate cyclase (sGC), to the heme-free and NO-insensitive apo-sGC. Therefore, other drug classes such as sGC stimulators and apo-sGC activators will be superior to NO donors for chronic use.

In a comorbidity model of stroke plus diabetes, a network pharmacology approach using subthreshold doses of a NOX and an NO synthase (NOS) inhibitor plus apo-sGC activator, resulted in a substantial neuroprotective effect. This approach is now in clinical trials. Also in diabetes, NADPH oxidase 5 (NOX5) was found as the most direct neighbour to NO-cGMP-related proteins. This connection was functionally validated both in a subgroup of hypertensive patients and in NOX5-knock in mice where NOX5 induced NOS uncoupling as a causal mechanism to induce age-related hypertension. Collectively, network pharmacology targeting causal disease modules represents a new approach to precisely define, diagnose and cure hitherto complex comorbidities such as diabetes, atherosclerosis, hypertension and stroke. Further validations in clinical trials is needed and planned to start in late 2020.